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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Abramovici et al.

Serial No.: 09/446,601

Filed: 03 April 2000

Group Art Unit: 1614

Examiner: D. Jagoe

For: Solid Pharmaceutical Composition Containing Benzofuran Derivatives

CERTIFICATE UNDER 37 C.F.R. 1.8(a)

I hereby certify that this correspondence is being deposited on the date indicated below with the United States Postal Service as first class mail addressed to:

Commissioner for Patents
Washington, DC 20231.

Geraldine Allen
Name

Nov. 26, 2002
Date

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

RESPONSE

This is responsive to the Office Action mailed June 4, 2002, in the above-identified application. The Office Action set a three-month shortened statutory period for response expiring September 4, 2002. The period for response is extended three months to December 4, 2002, pursuant to the Petition for Extension of Time under 37 C.F.R. 1.136(a) submitted herewith. This response is therefore timely.

In the instant Office Action, the rejection of claims 1-22 under 35 U.S.C. § 103(a) made in the previous Office Action (Paper No. 8) is maintained. In addition, claims 1, 2-6, 8-10, 13-15, and 17 are newly rejected under 35 U.S.C. § 102(b) as anticipated by Martin-Algarra et al., and claims 2, 7, 11, 12, 16, and 18-22 are newly rejected as unpatentable under 35 U.S.C. § 103(a) over Martin-Algarra.

In the previous Office Action, claims 1-22 were rejected as being unpatentable over a mosaic of three references, viz. the PDR in view of Story et al. and Martin-Algarra et al. In the present Office Action, it is stated that the Examiner is in agreement with Applicants' arguments regarding the Story et al. reference, i.e., that there is nothing in Story et al. that

would have suggested using such a small amount of non-ionic hydrophobic surfactant to both increase rate and reduce variability of absorption of either NSAIDs or amiodarone and dronedarone. Insofar as Story et al. is inadequate as a reference, the cited combination of references, of which it is an essential component, is likewise inadequate and the rejection based thereon must fall. Thus, in light of the Examiner's stated view of the Story et al. reference, it is not seen how the previous rejection which is based on the PDR in view of Story et al. and Martin-Algarra et al. together can be maintained. Accordingly, withdrawal of the rejection is respectfully requested.

As to the new rejections raised in the present Office Action, both are based on the Martin-Algarra reference alone. The Examiner states that the instant claims are drawn to a pharmaceutical composition comprising amiodarone hydrochloride in an oral formulation, such as a tablet and gelatin capsule, with the nonionic hydrophilic surfactant, polysorbate 80; and that concentrations of from 1% to 50% by weight, 1% to 20%, or 5% to 15% by weight of the active principle in base form are claimed. It is urged that Martin-Algarra et al. teach oral administration of amiodarone with polysorbate 80; that the absorption rate constants of amiodarone decreased as the surfactant concentration increased, absorption being unusually fast at lower surfactant concentrations; that the concentration appears to be 0.75 mg dissolved in 10 ml, which would be 7.5%, by weight of the active principle in base form; and that a solid dispersion is recited. The rejections are respectfully traversed and reconsideration thereof is requested.

The Martin-Algarra reference discloses the use of an *in situ* rat gut technique in which a solution of polysorbate 80 containing amiodarone hydrochloride was perfused directly into the rat intestine to study intestinal absorption of amiodarone. Clearly, this is not oral administration nor is it the administration, oral or otherwise, of a solid composition. Thus, the reference nowhere disclosed either oral adminstration or a solid pharmaceutical

composition for oral administration. The Examiner refers to a "solid dispersion" recited at page 6, column 2, of the reference. Actually, the language referred to states that

> "...the previously reported conclusions about the convenience of designing more reliable forms of amiodarone, containing a suitable dose of surfactant as a solid dispersion or similar preparation, have been entirely confirmed here."

No explanation or description of the "reported conclusions" is given nor is there any description of the composition or properties of a "solid dispersion" or of a method for the preparation thereof. Applicants make clear that a solid pharmaceutical composition refers essentially to a composition formed entirety of pulverulent solid ingredients which can be tabletted at room temperature comprising the active principle and the excipients, these ingredients being essentially in powder form, and that the so-called semi-solid pharmaceutical compositions formed of substances in pasty or waxy form when they are brought to moderate temperature (<70° C) do not form part of the invention (specification, page 1, lines 25-35). Clearly, nothing in Martin-Algarra discloses such "solid pharmaceutical composition".

The Examiner further points out that concentrations of from 1% to 50%, 1% to 20%, or 5% to 15% by weight of the active principle are claimed and that Martin-Algarra discloses a concentration of 0.75 mg in 10 ml, i.e., 7.5% by weight of the active principle. In fact, the percentages 1% to 50%, 1% to 20%, and 5% to 15% referred to by the Examiner are not percentages of active principle but rather are percentages of nonionic hydrophobic surfactant relative to the active principle. The concentration of 0.75 mg dissolved in 10 ml disclosed in Martin-Algarra refers to the concentration of amiodarone hydrochloride in the perfusion fluid in which the polysorbate 80 concentration ranged from 0.4 mM to 80 mM. These concentrations correspond to 0.075 mg/ml of amiodarone hydrochloride and 0.5 to 105 mg/ml of polysorbate 80. Accordingly, and as previously pointed out, the polysorbate 80 was present in a proportion of 666% to 140,000 % by weight of the amiodarone hydrochloride.

The reference therefore cannot possibly teach or suggest Applicants' formulations containing from 1% to 50% by weight of surfactant relative to the active principle. Moreover, the reference specifies that the lowest concentration of surfactant tested [i.e., 0.4 mM (0.5 mg/ml) or 666% relative to the active ingredient] is the concentration that "provides the minimal amount of surfactant leading to amiodarone solubilization" (page 5, column 1) and, therefore, actually teaches away from Applicants' invention. Accordingly, it is submitted that the Martin-Algarra reference fails to either teach or suggest Applicants' claimed invention and is therefore inadequate to support the rejections based thereon.

Lastly, as regards the double patenting rejection made in the previous Office Action and repeated in the instant Action, the '778 patent is drawn to parenteral solution formulations whereas the instant application is drawn to solid compositions for oral administration. Applicants' solid compositions, as described in the specification at page 1, lines 25-35, clearly do not include solutions. Hence, there is nothing in U.S. Patent 6,143,778 that would render the instant claims obvious, and the patent is not a proper basis for a double patenting rejection.

There being no remaining issues, this application is believed to be in condition for favorable reconsideration and early allowance and such actions are earnestly solicited.

Respectfully submitted,

Dated: 11/26/02

PAUL E. DUPONT
Registration No. 27,438

Sanofi-Synthelabo Inc.
Patent Department
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355
Tel.: (610) 889-6338
Fax: (610) 889-8799

Sanofi-Synthelabo Research
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

sanofi-synthelabo

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	U.S.P.T.O.	FAX#:	1-703-746-5062
FROM:	Geraldine D. Sbei	PHONE#:	610-889-6306
	Paralegal- Intellectual Property	FAX#:	610-889-8799
	Sanofi-Synthelabo		
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◊MESSAGE◊

As per your request, I am transmitting the following:

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November 26 , 2002

Response; Petition for Extension of Time under 37 CFR § 1.136(a) [in duplicate]

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